

Supplementary Tables

Supplementary Table 1 SNP-based heritability estimates for ADHD and lifetime cannabis use

For each disorder N effective, LD score regression heritability (h^2) with standard error (SE), intercept with standard error (Intercept (SE)) and ratio, obtained as (intercept-1)/(mean(chi^2)-1), with standard error (Ratio (SE)) are presented.

Trait	N effective	$h^2(\%)$	SE	Intercept (SE)	Ratio (SE)
ADHD	49017.41	25.98	0.02	1.03 (0.01)	0.11 (0.04)
Cannabis use	31933.13	9.14	0.02	1 (0.01)	< 0

Supplementary Table 2 Cross-trait single variant analysis top hit results

Fixed effects and random effects meta-analysis results are presented for SNPs meeting genome-wide significance ($P < 5 \times 10^{-8}$) in the fixed effects meta-analysis. In bold potential new signals represented by SNPs that did not meet genome-wide significance either in ADHD or cannabis use.

rs (chr:pos)	Gene (annotation)	Effect allele/	Fixed effects		Random effects		I^2 statistic	ADHD* OR (P-value)	Cannabis use OR (P-value)
			Other allele	OR (95% CI)	P-value ¹	OR (95% CI)			
rs2782639 (1:44006339)	<i>PTPRF</i> (intronic)	A/G	0.93 (0.91, 0.95)	2.29E-08	0.94 (0.9-0.98)	4.01E-03	64.17	0.92 (2.87E-08)	0.96 (8.47E-02)
rs11210887 (1:44076019)	<i>PTPRF</i> (intronic)	A/G	0.92 (0.9, 0.94)	2.71E-11	0.92 (0.89-0.96)	4.14E-06	40.64	0.91 (1.48E-10)	0.94 (1.44E-02)
rs56319043 (1:44171211)	<i>KDM4A-AS1</i> (intronic)	T/C	0.92 (0.9, 0.95)	3.87E-09	0.94 (0.86-1.03)	1.83E-01	89.63	0.9 (1.37E-11)	0.99 (6.00E-01)
rs113551349 (1:44475123)	<i>SLC6A9</i> (intronic)	T/C	0.91 (0.88, 0.93)	4.54E-10	0.94 (0.84-1.05)	2.76E-01	76.92	0.9 (1.05E-10)	1.01 (8.96E-01)
rs2391769 (1:96978961)	intergenic	A/G	0.94 (0.92, 0.96)	2.78E-08	0.94 (0.9-0.98)	2.87E-03	62.01	0.93 (1.04E-07)	0.96 (7.61E-02)
rs4858253 (3:20729091)	intergenic	T/C	0.94 (0.92, 0.96)	2.12E-08	0.94 (0.92-0.96)	2.12E-08	0	0.93 (5.52E-08)	0.95 (1.23E-02)
rs145108385 (5:43054747)	<i>LOC648987</i> (intronic)	A/G	1.08 (1.05, 1.1)	3.30E-08	1.08 (1.05-1.1)	3.30E-08	0	1.08 (1.58E-07)	1.06 (3.99E-02)
rs4916723 (5:87854395)	<i>LINC00461</i> (intronic)	A/C	0.93 (0.91, 0.95)	1.51E-09	0.94 (0.9-0.97)	6.80E-04	57.15	0.93 (1.81E-08)	0.96 (5.04E-02)
rs1476535 (7:114071035)	<i>FOXP2</i> (intronic)	T/C	1.07 (1.05, 1.1)	5.77E-10	1.07 (1.05-1.1)	5.77E-10	0	1.07 (3.14E-07)	1.06 (3.41E-03)
rs2189012 (7:114211912)	<i>FOXP2</i> (intronic)	A/G	1.07 (1.05, 1.1)	1.06E-08	1.07 (1.05-1.1)	1.06E-08	0	1.08 (3.89E-07)	1.06 (1.76E-02)
rs76545266 (8:34081521)	intergenic	T/C	0.85 (0.8, 0.9)	2.30E-08	0.85 (0.8-0.9)	2.30E-08	0	0.85 (1.23E-06)	0.87 (2.01E-02)
rs74760947 (8:34352610)	intergenic	A/G	0.84 (0.79, 0.88)	2.28E-10	0.84 (0.79-0.88)	2.28E-10	0	0.84 (1.39E-08)	0.87 (1.32E-02)
rs139868495 (8:34662970)	intergenic	T/C	1.19 (1.12, 1.26)	8.41E-09	1.19 (1.12-1.26)	8.41E-09	0	1.18 (1.10E-07)	1.18 (6.93E-02)
rs4259397 (8:93366290)	intergenic	A/G	0.93 (0.91, 0.96)	4.52E-08	0.93 (0.91, 0.96)	4.52E-08	0	0.93 (3.68E-06)	0.94 (6.20E-03)
rs797267 (12:89767237)	Intergenic	A/G	0.91 (0.89, 0.94)	3.51E-09	0.91 (0.89, 0.94)	3.51E-09	0	0.91 (1.69E-07)	0.92 (1.42E-03)
rs8039398 (15:47730870)	<i>SEMA6D</i> (intronic)	T/C	0.93 (0.91, 0.95)	3.94E-11	0.93 (0.91, 0.95)	3.94E-11	0	0.92 (2.99E-09)	0.94 (2.85E-03)

¹Full PGC+iPSYCH

Supplementary Table 3 Conditional analysis for signals in regions already reported in the PSG+iPSYCH meta-analysis on ADHD

Unconditional and conditional cross-trait results are presented for seven genome-wide significant variants in loci already identified in the PGC+iPSYCH meta-analysis with a different sentinel variant. Cross-trait sentinel variant results were conditioned on PGC+iPSYCH sentinel variants.

rs (chr:pos) ²	Original study	Effect allele	Unconditional Analysis		Conditional Analysis		LD r
			Beta (SE)	P	Beta (SE)	P	
rs2391769 (1:96978961)	Cross-trait	A	-0.07 (0.01)	2.78E-08	-0.06 (0.01)	3.67E-06	0.25
rs1222067 (1:96597502)	ADHD	A	-0.06 (0.01)	4.52E-06			
rs4858253 (3:20729091)	Cross- trait	T	-0.07 (0.01)	2.12E-08	-0.05 (0.01)	2.64E-04	-0.46
rs4858241 (3:20669071)	ADHD	T	0.06 (0.01)	1.83E-07			
rs2189012 (7:114211912)	Cross- trait	A	0.07 (0.01)	1.06E-08	0.04 (0.02)	5.38E-03	-0.61
rs10231382 (7:114096846)	ADHD	A	-0.07 (0.01)	6.90E-10			
rs1476535 (7:114071035)	Cross- trait	T	0.07 (0.01)	5.77E-10	0.04 (0.02)	3.24E-02	-0.82
rs10231382 (7:114096846)	ADHD	A	-0.07 (0.01)	6.90E-10			
rs76545266 (8:34081521)	Cross- trait	T	-0.16 (0.03)	2.30E-08	0.01 (0.07)	8.54E-01	0.92
rs74760947 (8:34352610)	ADHD	A	-0.18 (0.03)	2.28E-10			
rs139868495 (8:34662970)	Cross- trait	T	0.17 (0.03)	8.41E-09	0.05 (0.05)	2.91E-01	-0.87
rs74760947 (8:34352610)	ADHD	A	-0.18 (0.03)	2.28E-10			
rs797267 (12:89767237)	Cross- trait	A	-0.09 (0.02)	3.51E-09	-0.06 (0.02)	2.00E-04	-0.53
rs1427829 (12:89760744)	ADHD	A	0.06 (0.01)	3.86E-08			

²Since ADHD studies were imputed using 1000 Genomes Phase 3 reference panel (1) and lifetime cannabis use studies were imputed using 1000 Genomes Phase 1 reference panel (2), two PGC+iPSYCH sentinel variants (rs1222063 and rs5886709) were not included in the cannabis use meta-analysis and proxy variants (rs1222067, $r^2=0.701905$ with rs1222063) and rs10231382, $r^2=0.958662$ with rs5886709) were considered.

Supplementary Table 4 Cross-trait gene-based analysis top hit results

Gene-based results using fixed and random effect meta-analysis results for genes that met a Bonferroni corrected threshold for the number of genes analysed ($P < 2.79 \times 10^{-6}$) in the fixed effects meta-analysis are presented. Gene-based results for single trait analyses are also provided on the table for comparison. In bold new signals represented by SNPs that did not meet genome-wide significance either in ADHD or cannabis use.

Gene (chr:start-end)	SNPs (N)	Fixed effects		Random effects		ADHD ³ P-value	Cannabis use P-value
		Z	P-value	Z	P-value		
WDPCP (2:63338518-63825867)	704	4.76	9.67E-07	4.59	2.22E-06	2.04E-04	1.04E-02
<i>SLC9A9</i> (3:142974063-143577373)	1165	5.01	2.68E-07	4.04	2.62E-05	2.84E-04	8.56E-03
TMEM161B (5:87475450-87574665)	91	4.80	8.12E-07	4.59	2.24E-06	3.00E-06	1.17E-01
ZNF251 (8:145936294-145991285)	33	4.65	1.62E-06	4.63	1.86E-06	1.92E-05	5.79E-03
ZNF517 (8:146014261-146045461)	30	4.56	2.52E-06	4.41	5.19E-06	3.67E-05	1.79E-03

³Full PGC+iPSYCH results

Supplementary Table 5 Sign test results for ADHD and cannabis use

Results for the sign test are presented for variants associated with ADHD, assessing the direction of effect in cannabis use and for variants associated with cannabis use assessing the direction of effect in ADHD.

P-value threshold	All SNPs (N)	SNPs showing the same sign (N)	Proportion SNPs with the same sign (%)	95% CI	P-value
ADHD					
5.00E-08	12	10	83.33	(50.88, 97.06)	4.33E-02
5.00E-07	38	26	68.42	(51.21, 81.96)	3.50E-02
5.00E-06	72	48	66.67	(54.47, 77.07)	6.72E-03
5.00E-05	265	135	50.94	(44.77, 57.09)	0.81
Cannabis use					
5.00E-08	NA	NA	NA	NA	NA
5.00E-07	1	0	0	(0, 94.54)	1
5.00E-06	9	6	66.67	(30.92, 90.96)	0.50
5.00E-05	70	31	44.29	(32.59, 56.61)	0.40

Supplementary Table 6 ADHD and cannabis use results and IVW causal effect estimates for the 12 variants with P<5x10⁻⁸ in ADHD used in the Mendelian randomization analysis

rs (chr:pos)	Gene (annotation)	Effect allele	Other allele	ADHD ⁴			Cannabis use			IVW causal effect
				Beta	SE	P-value	Beta	SE	P-value	
rs2819330 (chr1:44002957)	<i>PTPRF</i> (intron)	A	G	0.0848	0.0154	3.60E-08	0.0393	0.0229	8.56E-02	0.4636
rs17531412 (chr1:44182244)	<i>ST3GAL3</i> (intron) ⁵	A	G	0.1029	0.0151	8.70E-12	0.0070	0.0219	7.48E-01	0.0680
rs3952787 (chr1:44323244)	<i>ST3GAL3</i> (intron) ⁵	T	C	0.0914	0.0155	3.59E-09	0.0368	0.0668	5.82E-01	0.4025
rs2391769 (chr1:96978961)	Intergenic	G	A	0.0785	0.0142	3.64E-08	0.0373	0.0210	7.61E-02	0.4753
rs227378 (chr4:103620385)	<i>MANBA</i> (intron)	A	C	0.0860	0.0149	7.48E-09	-0.0179	0.0281	5.24E-01	-0.2082
rs4916723 (chr5:87854395)	<i>LINC00461</i> (intron)	C	A	0.0832	0.0141	3.24E-09	0.0432	0.0221	5.04E-02	0.5192
rs9969232 (chr7:114158954)	<i>FOXP2</i> (intron)	A	G	0.0847	0.0148	1.05E-08	0.0584	0.0229	1.07E-02	0.6897
rs74760947 (chr8:34352610)	Intergenic	G	A	0.1887	0.0321	4.23E-09	0.1442	0.0582	1.32E-02	0.7641
rs704061 (chr12:89771903)	Intergenic	C	T	0.0765	0.0138	2.60E-08	0.0314	0.0205	1.25E-01	0.4102
rs281297 (chr15:47685504)	<i>SEMA6D</i> (intron) ⁵	C	T	0.0834	0.0149	2.20E-08	-0.0022	0.0237	9.25E-01	-0.0264
rs8039398 (chr15:47730870)	<i>SEMA6D</i> (intron) ⁵	C	T	0.0820	0.0137	2.42E-09	0.0594	0.0199	2.85E-03	0.7247
rs212178 (chr16:72578131)	intergenic	G	A	0.1197	0.0208	8.86E-09	0.0063	0.0349	8.56E-01	0.0526

⁴Restricted PGC+iPSYCH results excluding Spain and Yale-Penn results

⁵Correspond to independent signals ($r^2 < 0.05$, estimated using 1000 Genomes)

Supplementary Table 7 Mendelian randomization heterogeneity test

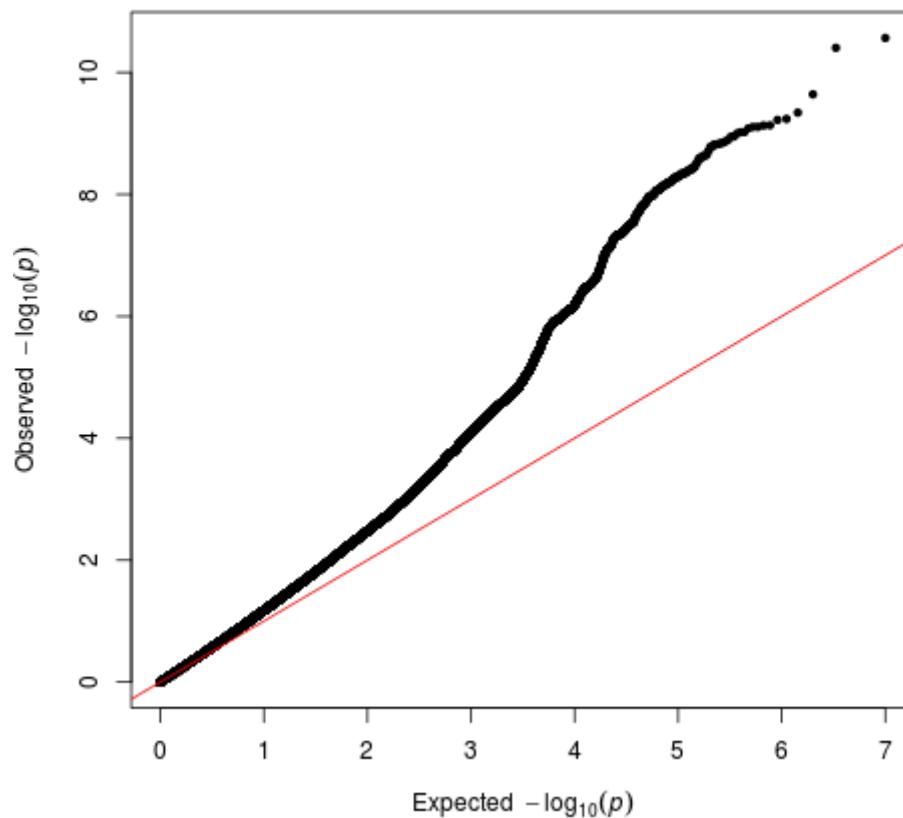
Chi-square statistics and P-values are presented for each of the four Mendelian randomization analysis designs using the inverse-variance weighted method.

Analysis design	P-value threshold	Chi-square	P-value
ADHD exposure cannabis use outcome	5x10-8	14.05	0.23
	5x10-6	63.23	0.73
Cannabis use exposure ADHD outcome	5x10-6	7.86	0.45
	5x10-5	81.27	0.15

Supplementary Figures

Supplementary Figure 1 Quantile-quantile plot of the cross-trait analysis of ADHD and cannabis use

The plot shows $-\log_{10}(P\text{-value})$ of expected results in case of no association against observed genome-wide association results.



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